REMARKS

Claims 1, 4-10 and 12-21 were pending and examined in the December 1, 2004 Office action. In this reply, claims 1, 8 and 12-14 have been amended and claims 4, 15, 16, 18, and 20-21 have been canceled without prejudice. Accordingly, claims 1, 5-10 and 12-14, 17 and 19 will be pending upon entry of this amendment.

The claims have been amended herein to recite methods using anti-gp39 antibodies or fragments that bind to an epitope which is specifically bound by the 24-31 antibody. An Affidavit of Randolph J. Noelle Ph.D. executed on July 26, 1998 is being provided herewith (**Exhibit D**). The Noelle Declaration, previously submitted in EP 0 721 469 B1, demonstrates important functional differences between the 5c8 antibody of Lederman et al. and the 24-31 antibody. These data support Applicants' position that the use of antibodies that bind the 24-31 epitope for preventing T cell mediated tissue destruction or autoimmune responses associated with type I diabetes is not taught or suggested by the prior art.

Rejection Under 35 U.S.C. §112-Written Description

Claims 1, 4-10 and 21 stand rejected under 35 U.S.C. §112 for allegedly lacking written support for the terms "cell-mediated immune reaction" to "one or more autoantigens." The Examiner alleges that the specification at pages 3-4 does not adequately describe the aforementioned, underlined terms. By this amendment, to expedite prosecution, claim 1 has been amended to recite "T cell mediated" in lieu of "cell mediated," thereby obviating this rejection. However, for the record, quoted below is the pertinent description from page 3, lines 25-36, which explicitly describes these terms (emphasis added):

> The language "autoimmune disorder" is intended to include disorders in which the immune system of a subject reacts to **autoantigens**, such that significant tissue or cell damage occurs in the subject. The terms "**autoantigen**" and "self-antigen" are used interchangeably herein...The term "self" as used herein is intended

> to mean any component of a subject and includes molecules, cells, and organs. **Autoantigens** may be peptides, nucleic acids, or other biological substances. The language "T cell mediated autoimmune disorder" is intended to include autoimmune disorders in which the reaction to self primary involves **cell-mediated immune** mechanisms as opposed to humoral immune mechanisms. Thus, the methods of the invention pertain to treatments of autoimmune disorders in which tissue destruction is primarily mediated through activated T cells and immune cells other than B lymphocytes.

The term "cell-mediated" is clearly supported by the above description. It is also asserted that the term "autoantigens," as well as the specific embodiments of autoantigens, are **plural**, therefore supporting the term "one or more." Moreover, at page 9, Example 1, the specification discloses that MBP, PLP, **or** MOG, i.e., **three (3)** autoantigens, can induce the T cell mediated autoimmune disease EAE in mice. Thus, administration of an anti-gp39 antagonist would prevent autoreactive T cell activation regardless of whether one, two, or all three of the foregoing antigens were used for induction of the autoreactive T cell population.

It is well-established law that the specification does not have to provide *in haec verba* support (exact words) for the claimed subject matter at issue as long as one of ordinary skill in the art would discern the limitation from the disclosure. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 56 USPQ2d 1481 (Fed. Cir. 2000). See also *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 54 USPQ2d 1277 (Fed. Cir. 2000) (The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognized that the inventor had possession of the claimed invention). One of ordinary skill in the art would have certainly recognized from the specification that the presently claimed method of inhibiting activated T cells to autoantigens would be effective against all autoreactive T cells would encompass a T cell mediated immune reaction to one or more autoantigens.

Accordingly, it is submitted that the terms "cell mediated" and "one or more autoantigens" are sufficiently supported in the specification and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. 112-Enablement

Claims 1, 4-10, and 12-21 stand rejected as allegedly lacking enablement, apparently due to lack of human *in vivo* data in the specification. According to the Examiner, *in vitro* and animal model studies have not correlated well with human clinical trials. On page 3 of the Office Action, the Examiner elaborates by providing a number of reasons why the gp39 antagonist may not be efficacious in humans.

While the latter certainly *may* be true in many instances, since drugs often fail in advanced, large-scale phase 3 studies for numerous reasons, the standard for patentability is **not the same** as the standard for regulatory marketing approval. While marketing approval is contingent upon efficacy in the target human population, by contrast, it has been held that pharmaceutical patent applications **do not** have to satisfy FDA standards in order to satisfy requirements under the patent law. *In re Hartop* 311 F.2d 249, 257-258 (C.C.P.A 1962). In distinguishing the standards for FDA approval from patent law standards, the court in *Hartop* noted that the Patent Office requirements for patent procurement are "quite different" than the statutory authority granted to the FDA or other Federal agencies· *Id.* See also *In re Anthony* 414 F.2d 1383 (C.C.P.A. 1969) (noting that safety is a relative matter and the FDA, not the Patent Office, has primary responsibility for determining the safety of drugs for marketing).

The above standard has been consistently adhered to by the Federal Circuit, which has gone even further and held that is accepted and well established that data obtained *in vivo* in animals, such as mice, establishes a reasonable expectation of a similar result in humans (i.e., predictability), for patentability purposes. See *Scott v. Finney*, 34 F.3d 1058, 32 USPQ2d 1115 (Fed. Cir. 1994) ("Testing for the full safety and efficacy of a prosthetic device is more properly

left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of patent and trademark proceedings."). See also *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120.

In this case, the *in vivo* data presented in an established animal model of EAE enables the present claims according to patent law. The "unpredictability" that the Examiner contends renders the present claims nonenabled is relative to the subject matter to be enabled. It is asserted that some extent of unpredictability is necessarily present in every patent for a therapeutic agent that does not describe human data generated from testing thousands of patients. If therapeutic efficacy in humans were absolutely predictable, then there would be no reason for extensive clinical trials to be conducted.

Applicants submit that the mouse EAE model is a widely accepted animal model for cell-mediated autoimmune disease characterized by tissue destruction. This is further evidenced by the fact that there are 353 references on PubMed as of the filing date of the June 7, 1995 priority date of this application which employ or mention the EAE mouse as an animal model of cell-mediated autoimmunity. See **Exhibit A.**

In addition, the Examiner contends that it would have required undue experimentation by a skilled artisan to prevent type I diabetes since there was no effective way to diagnose diabetes prior to clinical manifestations of the disease, at which point some tissue destruction had already occurred. In response, Applicants contend, as the Examiner suggests on page 4 of the Office Action, that the claims are intended to read on preventing *further* tissue destruction during treatment for type I diabetes following diagnosis. Applicants contend that this is clear from the phrase "in need of such treatment" in claim 1. The Federal Circuit has held that subjects "in need" of treatment knowingly be administered the claimed treatment for an intended purpose, i.e.,

the individual treated must be aware of having type I diabetes prior to treating it. *Janssen v. Rexall Sundown*, 342 F.3d 1329 (Fed. Cir. 2003).

Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §112-Indefiniteness

A) Claims 8 and 12-20 stand rejected as indefinite for lacking proper antecedent basis for being broader than claim 1 (claims 12-20), or for being improperly dependent for failing to limit the subject matter of a previous claim (claim 8).

By this amendment, claims 1, 8 and 12-16 have been amended, thereby obviating the above rejections. Accordingly, withdrawal of these rejections is respectfully requested.

B) Claim 8 and 12-20 also stand rejected as indefinite for the phrase "binding characteristics," which the Examiner alleges is ill-defined and ambiguous.

By this amendment, claims 8 and 12 have been amended to remove this phrase, thereby obviating this rejection. Withdrawal of the rejections is therefore respectfully requested.

C) Claims 12-20 also stand rejected for the phrase "T cell mediated autoimmune responses associated with type I diabetes." The Examiner contends that this phrase is also ill-defined and ambiguous, and requests that the claims be amended to recite specific endpoints that can be measured.

This rejection is respectfully traversed for the following reasons. It is asserted that, as of the earliest filing date, T cell mediated autoimmune responses associated with type I diabetes were well known, and included e.g., insulinitis and pancreatic beta cell (a.k.a. islet cell) destruction (see attached abstracts by Gelber, Doukas, and Horio) as well as the increase of certain pro-

inflammatory cytokines which mediate the tissue destruction, such as interleukin-2 (IL-2) and interferon-gamma (IFNγ) (see attached abstract by Rabinovich).

Thus, it is respectfully asserted that this phrase is not indefinite. One of ordinary skill in the art would have known exactly what a "T cell mediate autoimmune response associated with type I diabetes" was as of the earliest filing date.

D) Claims 12-20 were rejected as indefinite for reciting "24-31" and "89-76" as the sole identifiers for the antibodies.

To address this rejection, claim 12 has been amended to recite the ATCC Accession Number for the claimed antibody. It is asserted that this added description now renders claim 12, and dependent claims 13-20 therefrom, sufficiently definite. Accordingly, withdrawal of this rejection is respectfully requested.

E) Lastly, claim 21 was rejected as indefinite. Claim 21 has been canceled without prejudice herein, thereby rendering this rejection moot.

Rejection Under 35 U.S.C §102(e)

Unspecified claims stand rejected as allegedly anticipated under §102(e) by U.S. 6,592,868, to Lederman. The Examiner indicates that if gp39-specific antibodies other than the exact antibody 24-31 are encompassed by the claims, then the '868 patent anticipates these claims.

Claim 12 also remains rejected as anticipated by the '868 patent since the Examiner contends that there is no difference between the '868 method and the presently claimed method. In response to Applicants' previous evidence indicating that the '868 antibody (5c8) failed in clinical trials to treat diabetes, in contrast to the presently claimed antibody, the Examiner pointed out that products of identical chemical composition cannot have mutually exclusive properties.

To clarify the record, Applicants fully concur that products which are chemically identical cannot have mutually exclusive properties. However, Applicants respectfully remind the Examiner that the 5c8 antibody is **not chemically identical** to the instantly claimed antibody. By contrast, the presently claimed antibodies are completely distinct from the 5c8 antibody, as they neither have the same amino acid sequence, nor do they bind to the same epitope on gp39, much less elicit the same *in vivo* effects (as evidenced by the therapeutic failure of hu5c8 and the superior activity of 24-31-described below). Accordingly, withdrawal of this rejection is respectfully requested.

Applicants make similar points regarding the Examiner's contention that the '868 patent anticipates claims encompassing other than the specific 24-31 antibodies disclosed. In their present form as currently amended, the claims recite that the antibodies are *specifically* 24-31, or an antibody or fragment binds to an epitope which is specifically bound by antibody 24-31. In other words, while most of the claims encompass antibodies other than 24-31 specifically, the antibodies (or fragments) must bind the same epitope of the gp39 antigen bound by this antibody. This clearly excludes the '868 5c8 antibody. As indicated in the *American Journal of Transplantation* article submitted in the previous response (**Exhibit B attached**), clinical studies of hu5c8 were halted due to thromboembolic events and failure of efficacy (5 out of 7 patients experienced graft rejection). The article also stated that the presently claimed antibody (IDEC-131/E6040) targets a different epitope than hu5c8 antibody in autoimmune diseases. Moreover, in contrast to hu5c8, the presently claimed humanized antibody exhibits no severe adverse events but is safe and well-tolerated in humans (see documents submitted at **Exhibit C, attached,** which was Exhibit B of previous response).

This disparity is due to the fact that the prior art 5c8 antibody and the presently claimed antibodies do not bind to the same epitope on gp39. In addition to **Exhibit B**, this is evidenced by a copy of a Declaration by inventor Dr. Randolph Noelle, dated July 26, 1998, which was submitted during prosecution of co-owned European patent application 94926659.7 (EP 0721 469 B1). In this Declaration, attached as **Exhibit D**, Dr. Noelle presents *in vitro* and *in vivo* data

comparing presently claimed antibody 24-31 with the 5c8 antibody. Paragraph 10 of the Declaration describes an experiment which demonstrates that 5c8 and 24-31 **do not** bind to the same epitope. While high concentrations of antibody 24-31 can completely prevent binding of 5c8 to gp39 (and itself-see Figure 3 of Declaration), high concentrations of 5c8 cannot prevent binding of 24-31 to gp39 (see Figure 4 of Declaration). According to the Declaration, these results support that the conclusion that the epitopes are proximate to each other, but are clearly distinct.

In addition, the Declaration describes further experiments, in paragraphs 11 and 12 of **Exhibit D**, which demonstrate significant differences *in vivo* between 5c8 and 24-31. The experiments described in paragraph 11 demonstrate that 24-31 is more effective in blocking the *in vivo* binding of CD40 to gp39 than is 5c8. Figure 5 shows that 24-31 blocked binding of CD40 to gp39 more efficiently than 5c8. Half-maximal blocking occurred at a concentration of 1.5 μg/ml for 24-31, compared with 2.5 μg/ml for 5c8.

The experiment discussed in paragraph 12 of **Exhibit D** shows that 24-31 is significantly more effective at inhibiting the proliferation of human peripheral blood B cells than 5c8. Half-maximal inhibition of B cell proliferation was achieved at a concentration of 0.16 μg/ml of antibody 24-31, in contrast to 0.45 μg/ml for antibody 5c8.

Accordingly, the presently caimed methods **cannot** be inherently anticipated by the '868 patent as the Examiner suggests. Inherent anticipation would require that the antibodies of the presently claimed methods *necessarily* have the same function *in vivo* as the prior art 5c8 antibody. An inherent function is one that the evidence makes clear is necessarily present; mere probabilities or possibilities are not enough. *Continental Can Co. USA v. Monsanto Co.,* 948 F. 2d 1264, 1268-69 (Fed. Cir. 1991). (If the natural result flowing from the operation of a process that was used would necessarily result in each of the claim limitations, then the later claimed invention was inherent and anticipated). As demonstrated by the submitted articles, none of the presently claimed antibodies cause thromboembolic events *in vivo* as does antibody 5c8,

precluding the requirement for inherent anticipation that the two antibodies *necessarily* have the same *in vivo* function.

Lastly, while the '868 patent is presumed valid (as the Examiner notes), this presumption is not relevant to the matter at hand. The '868 patent does not inherently anticipate the present claims for the further reason that the Examiner has not demonstrated that 5c8 prevents T cell mediated autoimmune responses associated with diabetes. Prior to being pulled from the clinic, the literature only describes use of 5c8 for prevention of allograft rejection of transplanted pancreatic islet cells in diabetic patients, not of preventing e.g, endogenous islet cell destruction. In addition, 5c8 was being evaluated in clinical trials (prior to being halted in 1999) for autoimmune diseases *other* than diabetes (Factor VIII inhibitor syndrome, immune thrombocytopenic purpura, and lupus nephritis - see the press release attached at **Exhibit E**). Therefore, the Examiner has not met his burden of demonstrating that use of antibody 5c8 inherently anticipates the presently claimed method.

On page 7, fifth paragraph (and again under the §102 rejection at page 6, paragraph 10, third sentence), the Examiner reiterates that this rejection may be withdrawn if Applicants conceded that the claimed method is not for preventing type I diabetes *per se*, but for preventing the symptom of T cell mediated tissue destruction associated with type I diabetes. As indicated above, and for the reasons asserted above, Applicants confirm that the latter is the subject matter intended to be encompassed by of the present claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103-Obviousness

Claim 1, 4-10, and 12-21 stand rejected as obvious over the '868 patent, in view of US 5,747,037 ("'037") to Noelle. The Examiner contends that mere disclosure of administering an anti-gp39 antibody for the treatment of diabetes, as per the '868 patent, would render the present

claims obvious in view of the '037 teaching that 24-31 antibody inhibits various immune responses.

According to the Examiner's reasoning, *any* anti-gp39 antibody described subsequent to the '868 patent would have been obvious to use for the treatment or prevention of *any* autoimmune disease, *and* with a reasonable expectation of success. This is clearly the incorrect legal standard for obviousness. If this were the case, then, for example, every SSRI developed subsequent to fluoxetine would have been unpatentable as obvious for the treatment of depression, for the reason that the subsequent SSRIs also blocked serotonin re-uptake at the 5-HT receptor.

By contrast, for the reasons outlined above, it is asserted that the presently claimed method, by employing gp39 antagonists having different chemical structures, different epitope-binding properties, and different *in vivo* effects when compared to 5c8, cannot be obvious over the '868 patent, by virtue of these differences. It is further submitted that the '868 patent is precluded for use as a reference in combination with the '037 reference since, in addition to describing a completely different antibody, it does not even hint at use of the antibody to prevent T cell mediated autoimmune responses. While the '868 patent discloses that 5c8 can bind to gp39 and inhibit humoral, antibody responses, absent a disclosure of T cell mediated autoimmune responses, there would be no motivation to combine the '868 patent with any reference that discloses inhibiting T cell mediated immune responses to arrive at the claimed invention. In fact, by the time the present invention was made[1], the skilled artisan was well aware that diabetes was a T cell mediated disease **and not** a B cell-mediated disease, and thus would not look to a reference that taught inhibition of B cells to treat autoimmune diseases for guidance. Accordingly, it is submitted that since no skilled artisan would seek to inhibit B cell responses to treat diabetes, the '868 patent cannot be used a proper reference, alone or in combination with any other reference that teaches modulating T cell mediated autoimmune responses, for use in an obviousness rejection.

[1] Note that the '037 patent issued as a continuation-in-part of an earlier application, which was also a c-i-p of another earlier application. The first publication of the earlier-filed applications published on March 9, 1995 as WO 96/06666.

Regarding the '037 patent to Noelle, the Examiner contends that the disclosure in '037 that the 24-31 antibodies inhibit various immune responses, including induction of T cell tolerance to autoantigens, renders the present claims obvious. The Examiner alleges that the oridinarily skilled artisan would have been motivated to substitute the '037 antibodies for the presently claimed method of treatment, especially in view of the '868 disclosure of anti-gp39 antibodies to inhibit immune responses. The Examiner further indicates that there would have been a reasonable expectation of success for preventing cell mediated immune responses and tissue destruction based on the prior art teachings.

This rejection is respectfully traversed. In the first instance, the '037 patent, while disclosing that a gp39 antagonist can induced **antigen specific** T cell tolerance when administered **in conjunction** with the antigen or antigen presenting cell (APC) to be tolerized, **does not** teach or suggest administering a gp39 antagonist to prevent T cell mediated autoimmune responses, much less tissue destruction associated with diabetes.

Even assuming *arguendo* that one of ordinary skill in the art may have be motivated to treat diabetes using a gp39 solely from the teachings of the '037 patent, the artisan would have followed the teachings of '037 and tolerized T cells using a specific diabetes antigen (such as an islet cell) prior to, or in conjunction with, administration of the gp39 antagonist. This method is not the subject matter of the present claims. Moreover, there is no suggestion in '037 that a T cell mediated response could be inhibited merely by administering the gp39 antagonist, without the antigen, especially for a disease not disclosed by the '037 patent, much less with any reasonable expectation of success. Therefore, it is asserted that the '037 patent does not render the present claims obvious.

Accordingly, there would have been no motivation to combine the '868 and '037 references, and neither improper combination of the patents, nor either patent alone would render the present claims obvious.

Lastly, as provided in the Noelle Declaration at **Exhibit D**, and in the articles at **Exhibits B** and **C**, the 24-31 antibody recited in the claimed methods exhibits superior results *in vivo* over the 5c8 prior art antibody. In addition to being therapeutically safe by not causing thromboses in patients to whom it is administered (contrary to hu5c8), the antibodies of the presently claimed methods block the binding of CD40 to gp39 *in vivo* more effectively than 5c8. Appropriate consideration of objective evidence of superior results of the presently claimed antibodies must be accorded. See *Stratoflex Inc. v. Aeroquip*, 713 F.2d at 1538 ("It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence arising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.")

In summary, Applicants respectfully submit that the cited prior art falls well short of suggesting, much less teaching the claimed invention as amended.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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